Applicants provide herewith a reference Abstract further substantiating the significant differences between hyperalgesia (pain) and inflammation. It is anticipated, upon review of this additional information, considered in view of Applicants' previous arguments, that this application should be in condition for allowance.

Essentially, the Examiner's maintained rejection is based on her conclusion that the prior art, which relates to a method for treating hyperalgesia, i.e., pain, would suggest the claimed method of treating inflammation. Applicants respectfully submit that this rejection is improper as compounds which are suitable for treating pain are not necessarily suitable for treating inflammation. Indeed, these arguments are supported by a Declaration of record, i.e., of Yann Mahe, an expert in the art, having substantial expertise in the area of inflammation and pro-inflammatory cytokines. Again, the Examiner is respectfully advised that it is wholly improper to believe that a compound which inhibits pain, even pain associated with inflammation, would have any significant effect on inflammation. Indeed, these are different processes which are therefore typically treated using different compounds.

In this regard, the Examiner is respectfully referred to Applicants' January 15, 1998 Reply, wherein Applicants discussed at length that pain cannot be equated to inflammation, and further cited pages from a textbook substantiating that drugs for suppressing inflammatory and immune reactions are typically distinct from compounds

used for treating analgesia, i.e., pain. For example, it should be noted that this Reply made reference to the paracetamol compound which, while possessing the ability to inhibit pain and to exhibit antipyretic effects, had absolutely no anti-inflammatory activity. This is simply because inflammation is a distinct phenomena from pain, notwithstanding the fact that inflammation may sometimes be associated with pain.

As yet, additional evidence of the well-known fact in the pharmacological art that pain cannot be equated with inflammation and, moreover, that it cannot be reasonably extrapolated that a compound which inhibits pain would have a similar effect on inflammation, Applicants provide herewith an Abstract by Hoffman and Schmelz from the Eur. *J. Pain*, 1999 3(2):131-139. This Abstract, which is from a very recent Journal, provides further evidence which substantiates that the time course of hyperalgesia and erythema in human skin (following UVA and UVB radiation) are distinct from inflammation. In fact, the authors note that these phenomena have different time courses, i.e., erythema and hyperalgesia exhibit a typical time course, and note that inflammatory mediators responsible for vasodilation are not the same as those for inducing hyperalgesia. This simply means that erythema and hyperalgesia act through different time courses because they are elicited by a different stimuli than inflammatory mediators which result in inflammation. Therefore, as this reference supports a conclusion that these phenomena act via different mechanisms, this further substantiates Applicants'

arguments that these phenomena typically must be treated differently. This is further substantiated by the Reply referenced *supra*, which provides examples of compounds which inhibit inflammation or pain, not both.

It would appear further that the Examiner has maintained the rejection because of her conclusion that a method for treating inflammation would overlap with a method for treating pain. In fact, she so indicated at a previous personal interview concerning this application. However, this conclusion cannot be substantiated upon a complete understanding of inflammation *vis-a-vis* pain. Indeed, inflammation is a very complex phenomena which is described at pages 1-2 of the subject application. Inflammation involves a set of biological reactions which involve a series of non-specific reactions which are triggered by various phenomena that are initiated by various stimuli that result in three phenomena, i.e., vascular, cellulovascular and tissue fibrosis. Localized inflammation is associated with swelling, pain, redness, and warmth. Also, inflammation is generally attributable to the infiltration of injured tissues by an edema or vasodilation of capillaries. Therefore, inflammation, while it may be associated with pain, has a much more complex physiology. In fact, inflammation is further complicated in the fact that it is mediated by various factors, including cytokines, chemotactic factors, as well as other factors which are involved in the inflammatory cascade, such as aracadonic acid, prostaglandin, and other compounds. Based on the complex physiology and elicitors of

inflammation, Applicants respectfully submit that the Examiner's conclusion that one of ordinary skill would reasonably conclude that a method of treating pain would correlate to a method for treating inflammation is wrong. This is simply not the case.

The Examiner is respectfully requested, upon consideration of these Remarks, to allow this application. Moreover, the Examiner is further respectfully requested that if she elects not to allow this case that she promptly contact the undersigned so that prosecution may be expedited. Further, if the Examiner has any questions in connection with this Reply, or any other matter, she is respectfully requested to contact the undersigned.

Respectfully submitted,

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